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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/865,420	05/29/2001	Mitsuru Ohkubo	205625US0CONT	6383

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,420	OHKUBO ET AL.	
	Examiner	Art Unit	
	Binta M Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-47 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-47 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

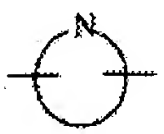
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The examiner notes the applicant's election of the compound of claim 21 at paper no. 7. The examined Group I genus is drawn claims 1-47, to the compounds claimed, process of preparing and a method of using the compound wherein R1 is saturated or unsaturated piperidine, substituted by X at the 4 position, wherein X is O, S, or NH, I is 0 or 1, A1 is lower alkyl optionally substituted with nonheterocyclic ring subtituents, m is 0 or 1, the



moiety is saturated or unsaturated piperidine substituted at the nitrogen with the y moiety and at the 3 position with A2 and optionally substituted nonheteroring substituents, Z is –(C(O)(R3)-, wherein R3 is H, or Ak, A3 is lower alkyl optionally substituted with nonheteroring substituents, R is carboxyl or protected carboxyl. This restriction is made FINAL.

The 112, first paragraph rejection made at paper no. 20 is withdrawn in light of applicant's comments in the amendment filed 4/5/04.

(new rejections)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject

matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention in claims 23-24 is the treatment of an any disease caused by thrombus formation with a compound of formula I.

The State of the Prior Art

The state of the prior art is that glocyprotein IIB/IIIa antagonists have been very disappointing and only minor therapeutic effects have been detectable, resulting in a slight reduction in schemic cardiac events. See Darious et. al. In all studies, there done in Darious, there was a slight trend towards an increased mortality in the glycoprotein IIB/IIIa receptor-antagonist-treated group of patients. See Darious et. al., In metal-analysis, a 35% relative increase in mortality has been calculated for patients being treated long term with the oral glycoprotein antagonists. See Darious et. al., The mechanism resulting in increased mortality is unknown, therefore, the clinical development of most of these drugs has been halted prematurely. See Darious

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of Glycoprotein IIB/IIIa-mediated diseases, whether the Glycoprotein IIb/IIIa was activated or inhibited would affect the possible treatment of any disease.

Hence, in the absence of a showing of correlation between all the conditions claimed as capable of treatment by the compound of claim 1 and the inhibition of Glycoprotein IIb/IIIa, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of Glycoprotein IIb/IIIa, i.e. whether promotion or inhibition would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present

The direction present in the instant specification is that the compounds of claim 1 can inhibit Glycoprotein IIb/IIIa which helps in the treatment for the diseases claimed. However, the specification is silent and fails to provide a correlation between the diseases listed and the inhibition of Glycoprotein IIb/IIIa.

The presence or absence of working examples

There are no working examples of these compounds on any of the claimed diseases. Also, the compounds which are disclosed in the specification have no pharmacological data regarding the treatment of any disease and have no data on the possible treatment of Glycoprotein IIb/IIIa -mediated diseases that require the activation or inhibition of Glycoprotein IIb/IIIa. Also, the specification fails to provide working examples as to how the listed diseases can be treated by the inhibition of Glycoprotein IIb/IIIa, i.e. again, there is no correlation between the diseases listed and inhibition of Glycoprotein IIb/IIIa.

The breadth of the claims

The breadth of the claims is that the compound of claim 1 can treat any disease caused by thrombus formation, without regards as to the affect of NO on the stated diseases.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what listed diseases would be benefited by the inhibition of Glycoprotein IIb/IIIa and would furthermore then have to

determine whether the claimed compounds would provide treatment of the disease by the inhibition of Glycoprotein IIb/IIIa.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claim 1 for the treatment of an Glycoprotein IIb/IIIa - mediated disease. As a result necessitating one of skill to perform an exhaustive search for which Glycoprotein IIb/IIIa -mediated diseases can be treated by the compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which NO-mediated diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome deleting claims 23-24.

Claims 39-41 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

A compound in a compound claim is presumed to already be isolated, purified, and chemically synthesized. This objection can be overcome by deleting these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-24, 39, 40, 41 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 23, lines 1-2, the phrase "a disease caused by thrombus formation" is ambiguous. What diseases caused by thrombus formation is the applicant claiming?

B. In claim 24, lines 1-4, the phrase "disease caused by thrombus formation is restonosis or reocclusion; the thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation or transplantation, disseminated intravascular coagulation, thrombotic htrombocytopenic, essential thrombocytosis or inflammation" is ambiguous because none of these conditions are diseases but are conditions. It is suggested that the term "disease" be changed to "conditions".

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 20 rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-2 of prior U.S. Patent No. 6538007. This is a double patenting rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20, 23-29, 39-47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 09865420. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims a species which anticipates the instant genus as well as the hydrochloride salts of species claimed in claims 25-29 and a method antagonizing glycoprotein IIb/IIIa activity with this species. The instant compounds are glycoprotein IIb/IIIa inhibitors.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20, 23-29, 39-47 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6384028. Although the conflicting claims are not identical, they are not patentably distinct from each other because the US patent claims a subgenus of the instant genus of compounds.

U.S. Patent No. 6384028 et. al. teaches the instant compound as shown in Formula I, where wherein R1 is tetrahydroisoquinolyl or tetrahydroisoquinolyl having an amino protective group, R2 is carboxy or protected carboxy, A1 is lower alkylene, lower alkanyl-ylidene, lower alkenylee, A2 is lower alkylene which

is optionally substituted, is peperidinediyl or tetrahydroisoquinolinediyl, me is an integer of 0 or 1, a pharmaceutical composition containing said compound, and a method of treating diseases caused by thrombus formation. At column 65, see the compound in claim 1. The difference between the prior art compound, a method of treating with this compound and a pharmaceutical composition containing said compound and the instantly claimed compounds, methods, and pharmaceutical composition is the teaching of a generic compound versus a disclosed species. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. For instance, see the compound, example 173, where a disclosed species is exemplified. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164

USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

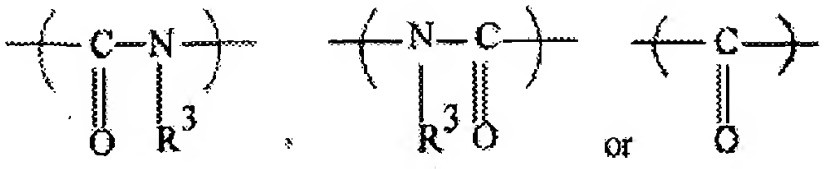
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20, 23-29, 30-47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6380215. Although the conflicting claims are not identical, they are not patentably distinct from each other because Patent 6380215 claims a genus which encompasses the instant subgenus, a method of preparing this genus, and a method of treating diseases caused by thrombus formation with the said compounds.

6380215 et. al. teaches the instant compound where wherein R1 is a 6-membered cycloalkyl containing 1 to 3 nitrogen atoms which may have one or more amino protective groups, X is O, S or NH, l is an integer of either 0 or 1; A1 is lower alkylene, lower alkenylene or lower alkanylylidene, each of which may have suitable substituents, Y is NH, and m is an integer of either 0 or 1;

is a 5 or six membered N-containing heterocyclic group containing 1 to 3 nitrogen atoms which may have one or more suitable substitutents, A2 is lower alkylene and n is an integer of either 0 or 1, Z is



wherein R3 is hydrogen

or lower alkyl, A3 is lower alkylene which has one or more suitable substitueents except carboxy and protected carboxy, with the proviso that when Z is –C(O)NH- that A3 is not lower lower alkylene substituted with aryl, aryl(lower alkyl or an unsaturated heterocyclic group, pharmaceutical compositions containing said compounds, the process of preparing these compounds and the method of treating diseases causd by thrombus formation using these compounds . At columns 81-82, see the compound in claim 1. The difference between the prior art compounds, methods of using, process of preparing, and pharmaceutical compositions, and the instantly claimed compounds, method of using, process of preparing, and pharmaceutical compositon is the teaching of a generic compound versus a disclosed species. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. For instance, see the compound, example 44, where a disclosed species is exemplified. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone

number is (703) 306-5437. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Alan Rotman can be reached on (703)308-4698. The fax phone numbers for the organization where this application or proceeding is assigned are (703)308-7922 for regular communications and (703)308-7922 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0193.

BMR
July 8, 2004

JOSEPH K. McKANE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600